(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 462 075 A2**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **91830170.6**

(51) Int. Cl.^{5} : **A61K 31/70**

(22) Date of filing : **26.04.91**

(30) Priority : **13.06.90 IT 4805790**

(43) Date of publication of application :
18.12.91 Bulletin 91/51

(84) Designated Contracting States :
DE FR GB

(71) Applicant : **POLIFARMA S.p.A.**
Via Tor Sapienza 138
I-00155 Roma (RM) (IT)

(72) Inventor : **Politi, Vincenzo**
77 Via Albano
I-00179 Roma RM (IT)
Inventor : **De Luca, Giovanna**
124 Via Ugo De Carolis
I-00136 Roma RM (IT)
Inventor : **Di Stazio, Giovanni**
221 Via Clivo di Cinna
I-00136 Roma RM (IT)
Inventor : **Materazzi, Mario**
10 Via Delleani
I-00155 Roma RM (IT)

(74) Representative : **Bazzichelli, Alfredo et al**
c/o Società Italiana Brevetti S.p.A. Piazza di Pietra, 39
I-00186 Roma (IT)

(54) Use of uridine in the pharmacological treatment of the peripheral complications of diabetes.

(57) Uridine is used to treat the peripheral complications of diabetes, such as neuropathy, retinopathy and vasculopathy, thanks to its characteristics of promotor of glycogen endocellular biosynthesis. 40 diabetic patients were treated for six months with uridine or with placebo in a double-blind clinical test.

EP 0 462 075 A2

The present invention refers to a new therapeutic use of uridine in the field of peripheral complications in diabetes mellitus.

Uridine is a known endogenous compound which has been studied in the past as a pharmacological agent in many experimental models, even those in no way related to each other. It has, in fact, been shown that cytidine and uridine are capable of prolonging the functional survival of an isolated cat brain. Other researchers have brought to light important anticonvulsive properties of uridine. More recently, uridine has been proposed as a substance promoting sleep, as a substitute for a renal natriuretic system, or as a dopaminergic modulator of the central nervous system.

It is furthermore universally known from classical biochemistry texts that uridine is the most important carrier of glucose within the cell, and that glycogen can only be formed upon intervention of uridine.

It has also been shown that cytidine and uridine are capable of consenting the normal use of glucose in cirrhotic patients treated with insulin. It has furthermore been shown that uridine increases the formation of glycogen in the muscles and that uridine can antagonize certain effects due to insulin hypoglycemia.

The peripheral complications in diabetes mellitus include a number of disabling situations, such as neuropathy, retinopathy, vasculopathy, etc. due to the presence in the blood of high quantities of glucose, which can spread passively in all types of cell not provided with specific "carriers".

If the endocellular glucose exceeds the energy requirement, and is not stored in the form of polysaccharides, it can damage the cell, both because it changes into fructose and sorbitol (sugars which do not easily spread outwards, and which for this reason cause the cell to swell and lose functional activity), and because it can react with proteins and nucleic acids, bringing about a form of premature "cell aging".

To relieve the peripheral symptomatology of diabetes mellitus, certain drugs have recently been proposed in the field of therapy. These drugs, by inhibiting the enzyme "aldosoreductase", prevent the glucose from transforming itself into sorbitol, thus limiting the damage caused by cellular oedema (see for example Annual Reports in Medicinal Chemistry 19, 169-177, 1984). At least in short-term clinical tests, these compounds have shown themselves to be of use to antagonize diabetic neuropathies (see for example: Lancet II, 758-762, 1983; New England J. Medicine 316, 599-606, 1987). However, these synthetic derivatives are not without side-effects which could compromise their long-term use, as in theory the diabetic patient would have to be treated all his life. It is therefore necessary to find physiological compounds that, as well as being active, are also free from serious undesirable effects.

It has now been surprisingly found, and forms the object of the present invention, that uridine possesses these properties and can be used to decrease the peripheral symtomology of diabetes, without causing side-effects even in the case of long-term treatment. Uridine can thus be administered to patients suffering from diabetes mellitus for the pharmacological treatment of peripheral complications such as neuropathy, retinopathy or vasculopathy.

It is thought that the uridine, which is able to enter with ease into the cells, can store the glucose present therein under the form of glycogen.

In order to evaluate at an experimental level the intervention of uridine upon the peripheral symptoms of diabetes, the following experimental tests have been performed.

Experimental pattern

Fourty diabetic patients (25 male and 15 female) were selected, having an average age of 48,5 ± 3,4 years, with a medical history of at least 5 years of diabetes, showing a reduction of the speed of motorial conductivity (VCM), and of the speed of sensorial conductivity (VCS) in at least one peripheral nerve, persistant pain in the lower limbs, reduction of the threshold of vibration perception.

After having undergone a "wash-out" period of two weeks, to suspend all pharmacological treatment that might interfere with the evaluation of the parameters to be examined, the patients were divided randomly into two groups: the first group received 300 mg of uridine three times per day; the second group received similar capsules containing placebo. Neither the patients nor the doctors knew who was being treated with placebo and who with uridine (double-blind test). Treatment continued for 180 consecutive days.

Clinical and neurophysiological evaluation took place at the following times: prebasal, basal (after two weeks "wash-out"), at 60 days, 120 days and 180 days, and after 90 days from the end of treatment as a follow-up. All patients were evaluated after a general and neurological check-up, ECG (electrocardiogram), haematological, urine and glycosilate haemoglobin (HnAlc) tests. The statistical calculation was carried out using the Student test and with the two-way Anova test.

Results

None of the patients had to suspend treatment due to side-effects, and this gives an indication of the optimum tolleration of uridine, a fact which can also be seen from the absence of significant differences between the two groups as far as the haematological, ECG, urinary and glycosilate haemoglobin tests are concerned.

The statistical test showed differences both in the VCM and in the VCS. These differences became significant at the 120th day and remained so both at the 180th and during the follow-up period.

Table 1

Average VCM ± SD (m/sec) of the SPE in diabetics treated with uridine and with placebo.

	URIDINE	PLACEBO	Student	Anova
Pre-basal	38.1+1.8	38.4+2.3	N.S.	N.S.
Basal	37.4+2.3	38.0+2.7	N.S.	N.S.
Day 60	37.7+2.2	38.1+2.4	N.S.	N.S.
Day 120	40.9+2.4	38.2+2.4	p<0.05	p<0.01
Day 180	43.5+1.9	38.6+2.4	p<0.01	p<0.001
Follow-up	43.0+1.4	38.4+2.5	p<0.05	p<0.001

SPE = outer sciatic popliteal nerve

SD = standard deviation

Table 2

Average VCM ± SD (m/sec) of the SPI in diabetics treated with uridine and with placebo.

	URIDINE	PLACEBO	Student	Anova
Pre-basal	34.9+2.1	35.3+2.4	N.S.	N.S.
Basal	34.8+1.6	34.9+1.8	N.S.	N.S.
Day 60	35.7+1.8	35.5+1.9	N.S.	N.S.
Day 120	39.5+2.1	35.4+2.7	p<0.005	p<0.005
Day 180	42.4+1.6	35.8+1.7	p<0.0005	p<0.001
Follow-up	41.3+1.1	35.3+2.1	p<0.001	p<0.001

SPI = inner sciatic popliteal nerve

Table 3

Average amplitude ± SD (microV) of the motorial response of the SPI in diabetics treated with uridine and with placebo.

	URIDINE	PLACEBO	Student	Anova
Pre-basal	6.3+3.2	6.2+2.7	N.S.	N.S.
Basal	6.1+2.6	6.1+2.4	N.S.	N.S.
Day 60	6.4+2.6	6.3+2.5	N.S.	N.S.
Day 120	7.4+2.8	6.4+2.2	N.S.	p<0.01
Day 180	8.7+3.0	6.2+2.4	p<0.05	p<0.01
Follow-up	8.5+3.1	6.1+2.2	p<0.05	p<0.01

Table 4

Average VCM ± SD (M/sec) of the sural nerve in diabetics treated with uridine and with placebo.

	URIDINE	PLACEBO	Student	Anova
Pre-basal	32.6+3.0	32.7+3.2	N.S.	N.S.
Basal	32.8+2.0	33.0+2.5	N.S.	N.S.
Day 60	34.0+2.3	32.9+2.0	p<0.05	p<0.01
Day 120	37.2+2.2	33.4+2.6	p<0.005	p<0.001
Day 180	41.1+2.2	33.0+2.3	p<0.001	p<0.001
Follow-up	40.1+1.7	33.2+2.2	p<0.005	p<0.001

Table 5

Average amplitude ± SD (microV) of the SAP of the sural nerve in diabetics treated with uridine and with placebo.

	URIDINE	PLACEBO	Student	Anova
Pre-basal	4.5+1.9	4.7+2.3	N.S.	N.S.
Basal	4.4+1.8	4.8+2.4	N.S.	N.S.
Day 60	4.9+2.0	4.6+2.1	N.S.	N.S.
Day 120	5.9+2.0	4.7+1.9	p<0.05	p<0.05
Day 180	7.0+2.4	4.7+2.2	p<0.001	p<0.01
Follow-up	6.7+1.7	4.9+2.2	p<0.005	p<0.01

SAP = potential of sensorial action

Conclusions

The results reported above show that uridine is capable of reducing the entity of complications in diabetes mellitus in a group of patients treated for 6 months with the drug. The study was performed using a double-blind test and the results are derived from objective measures. It can thus be concluded that uridine, probably by means of the biosynthesis of glycogen within the cells, limits the damage caused by high levels of glucose, and can thus be used in the treatment of peripheral disturbances in diabetes, such as retinopathy, vasculopathy,

etc.

The daily dose can vary between 500 and 2000 mg per day of uridine taken orally and the dose can be administered using the normal pharmaceutical forms.

Claims

1. Use of uridine for the manufacture of a medicament for the pharmacological treatment of complications produced by diabetes mellitus in the peripheral nervous system or in the peripheral vascular system.

2. Use of uridine as claimed in claim 1, in which said complications of the peripheral nervous system is muscular neuropathy or retinopathy.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 462 075 A3**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number : **91830170.6**

(51) Int. Cl.^{5} : **A61K 31/70**

(22) Date of filing : **26.04.91**

(30) Priority : **13.06.90 IT 4805790**

(43) Date of publication of application :
18.12.91 Bulletin 91/51

(84) Designated Contracting States :
DE FR GB

(88) Date of deferred publication of search report :
15.01.92 Bulletin 92/03

(71) Applicant : **POLIFARMA S.p.A.**
Via Tor Sapienza 138
I-00155 Roma (RM) (IT)

(72) Inventor : **Politi, Vincenzo**
77 Via Albano
I-00179 Roma RM (IT)
Inventor : **De Luca, Giovanna**
124 Via Ugo De Carolis
I-00136 Roma RM (IT)
Inventor : **Di Stazio, Giovanni**
221 Via Clivo di Cinna
I-00136 Roma RM (IT)
Inventor : **Materazzi, Mario**
10 Via Delleani
I-00155 Roma RM (IT)

(74) Representative : **Bazzichelli, Alfredo et al**
c/o Società Italiana Brevetti S.p.A. Piazza di Pietra, 39
I-00186 Roma (IT)

(54) Use of uridine in the pharmacological treatment of the peripheral complications of diabetes.

(57) Uridine is used to treat the peripheral complications of diabetes, such as neuropathy, retinopathy and vasculopathy, thanks to its characteristics of promotor of glycogen endocellular biosynthesis. 40 diabetic patients were treated for six months with uridine or with placebo in a double-blind clinical test.

EP 0 462 075 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 83 0170

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	CHEMICAL ABSTRACTS, vol. 83, no. 3, 21st July 1975, page 52, abstract no. 22572d, Columbus, Ohio, US; C. SERRA: "Therapeutic effect of pyrimidine nucleosides on the central and peripheral nervous system", & GAZZ. MED. ITAL. 1974, 133(8-9), 390-400 * Abstract * ---	1,2	A 61 K 31/70
X	CHEMICAL ABSTRACTS, vol. 77, no. 3, 17th July 1972, page 65, abstract no. 14390d, Columbus, Ohio, US; C. SERRA: "Motor nerve conduction velocity of normal and arteropathic subjects subjected to chronic pharmacological treatment with pyrimidine nucleosides", & RIFORMA MED. 1971, 85(50), 1544-51 * Abstract * ---	1,2	
P,X	ZEITSCHRIFT FÜR ALLGEMEIN MEDIZIN, vol. 67, no. 6, 28th February 1991, page 346; C. SCHAPER: "Therapiekonzepte zur Behandlung des diabetischen Fusses" * The whole article * ---	1,2	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A 61 K
Y	WO-A-8 903 837 (PRONEURON, INC.) * Page 8, lines 1-14; page 14, line 3 - page 15, line 4; page 17, line 28 - page 18, line 32; page 21, line 35 - page 22, line 14; page 24, line 28 - page 25, line 12; page 26, lines 12-29; page 28, line 35 - page 29, line 15; page 35, line 22 - page 36, line 26; claims 1,2,10,11,15,16,21,26,30,32 * --- -/-	1,2	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11-11-1991	ORVIZ DIAZ P.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 83 0170

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	CHEMICAL ABSTRACTS, vol. 89, no. 14, 2nd October 1978, page 540, abstract no. 117822y, Columbus, Ohio, US; & RO-A-60 706 (INSTITUTUL DE CERCETARI CHIMICO-FARMACEUTICE) 05-04-1976 * Abstract * ---	1,2	
Y	CHEMICAL ABSTRACTS, vol. 89, no. 14, 2nd October 1978, page 540, abstract no. 117823z, Columbus, Ohio, US; & RO-A-60 705 (INSTITUTUL DE CERCETARI CHIMICO-FARMACEUTICE) 30-03-1976 * Abstract * -----	1,2	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11-11-1991	ORVIZ DIAZ P.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)